College of Health and Medical Technologies - Al-Dour
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The second stage

# pharmacology

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# Principles of Drug Administration

- Upon completion of this lecture, we will be able to
- 1. Discuss medication order and its contents
- 2. Define medication errors and explain general principles of drug administration to prevent the medication errors
- 3. Discuss the different routes of drug administration.

# Medication Orders and Prescriptions

- practitioner (health care professionals, usually doctors) for a specific medication to be administered to a patient.
- Typically a 'prescription' is used in the outpatient whereas medication 'order' is used in the inpatient (in hospitals). Traditionally a prescription is given to the patient to fill at a pharmacy.

# Prescription or medication

- order should include
- The full name of the patient; age; sex. (even address)
- − Name of the drug (preferably the generic); the dose, route, and frequency of administration; and duration of treatment.
- − Date, time, name and signature of the prescriber, usually a doctors.

# Medication Errors

- any occurrence (preventable event) that may cause or lead to inappropriate
- medication use or patient harm while the medication is in the control of healthcare professional, patient, or consumer.
- Medication errors are a major problem in health care today – major cause of morbidity and mortality.

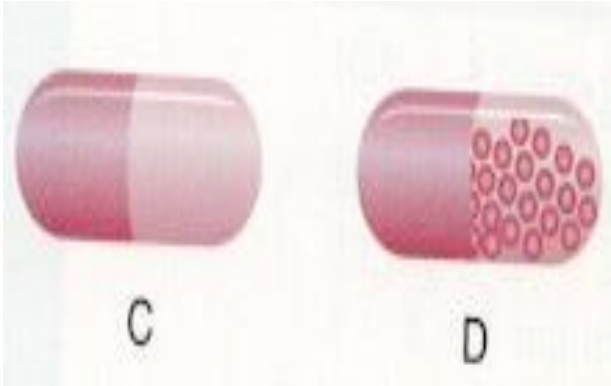
# Types of Medication Errors

- Medication errors fall into 13 major categories.
- Some types of errors cause harm directly, and some cause harm indirectly. For example, giving an excessive dose can cause direct harm from dangerous toxic effects.
- Conversely, giving too little medication can lead to indirect harm through failure to adequately treat an illness.

- 1. Wrong patient
- 2. Wrong drug
- 3. Wrong route
- 4. Wrong time
- 5. Wrong dose
- 6. Omitted dose
- 7. Wrong dosage form
- 8. Wrong diluent
- 9. Wrong strength/concentration
- 10. Wrong infusion rate
- 11. Wrong technique (includes inappropriate crushing of tablets)
- 12. Deteriorated drug error (dispensing a drug after its expiration date)
- 13. Wrong duration of treatment (continuing too long or stopping too soon)

# Source of medication errors

- Prescribers
- Pharmacist
- Nurses
- Drugs manufacturers Consumer/patients and their families
- Circumstances



# Drug Formulations and dosage forms

- Pharmaceutical Formulation:
- It is the method by which a drug is prepared – the process in which different chemical substances,
- including the active drug, are combined to produce a final medicine product.
- Dosage Form :It is the form in which the above formulation can be administered to a patient.
- e.g. as tablet, capsule, syrup or injection …etc.

# Drug Formulation and dosage forms

- according to the
- 1) Drug's chemical and physical characteristics,
- 2) Reason for use, and
- 3) Route of drug a administration .
- Some drugs are available in only one dosage form; others are available in multiple dosage forms — choosing a form that is best received by the patient will lead to a better total outcome.
- Most of drugs can be administered by a variety of routes – Major routes of drug administration include:
- 1) Enteral,
- 2) Parenteral, and
- 3) Topical

# Additional methods of administration

- Intra-lesional (into a lesion)
- Intra-thecal (instilling drugs directly into CSF) or intra-spinal
- Intra-cardiac (into the heart)
- Intra-arterial (administration is not by direct arterial injection but by means of a catheter that has been placed in an artery)
- Intra-articular (into a joint)
- Intra-pleural

# Factors that determine the choice of drug administration routes, include:

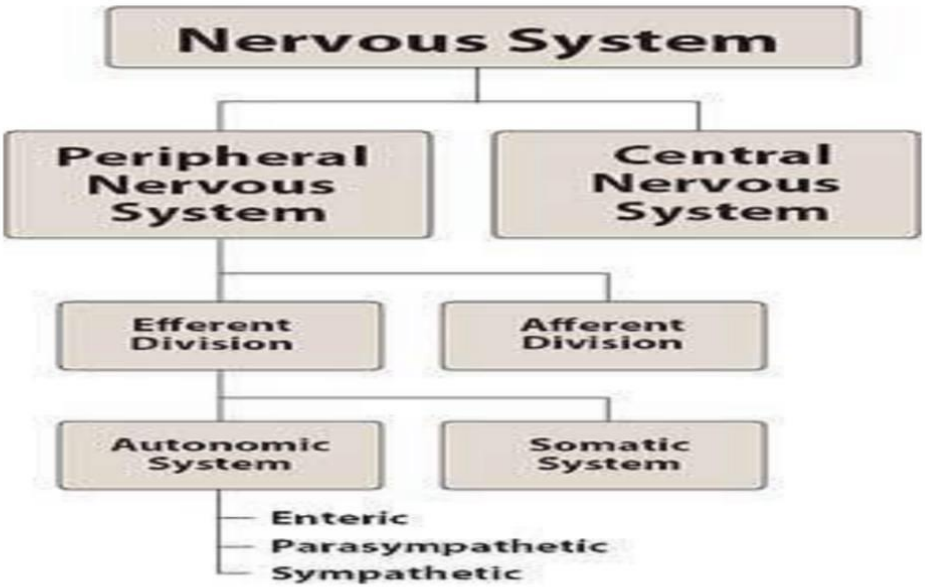
- 1) Physical and chemical properties of the drug (drug characteristics).
- 2) The formulations available (dosage form) in which the drug is available
- 3) Site of desired action, systemic or local effects
- 4) Rate and extent of absorption of the drug from different routes
- 5) Effect of digestive juices and first pass metabolism on the drug.
- 6) Rabidity with which the response is desired – onset of action (routine treatment or emergency).
- 7) Accuracy of dosage required (I.V. & inhalation can provide fine-tuning).
- 8) The patient's age and the clinical condition – unconscious, vomiting, etc. (Patient related factors or patient characteristics)
- 9) Which is the most convenient route is required for the patient and whether the patient is compliant or not

# Self-assessment

- Discuss medication order and its contents
- Define medication errors
- Explain general principles of drug administration to prevent medication errors
- What are responsibilities of nurses regarding Medication Errors?
- What are different routes of drug administration?
- What are factors that determine the choice of drug administration routes?
- Discuss Advantage and Disadvantage of different routes of drug administration

- Thank you for attention

**Organization**




**1. Somatic nervous system :**

Its innervate skeletal muscle Axon originate from spinal cord and release neurotransmitter Ach at neuromuscular junction Its voluntary Have no ganglia

**2.autonomic nervous system :**

Regulate the activity of

-smooth muscle

-cardiac muscle

- exocrine glands

2 neuron involved in the transmission process.

1st originate from the CNS and synapse in ganglia

2nd innervate the target tissue . Involuntary

## The autonomic nervous system subdivided into

**1- Sympathetic N.S.**

**2- Parasympathetic N.S.**

| | Location | Neurotransmitters | nerve | Receptors |
|---|---|---|---|---|
| Sympathetic | Thoracolumbar portion of the spinal cord | Epinephrine Norepinephrine | Adrenergic neurons<br>1-Preganglionic N. release Ach into nicotinic R. OF postganglionic N.<br>2-postgangilonic N. release NE into the effectors tissue | α 1<br>α 2<br>β 1<br>β 2<br>β 3 |
| Parasympathetic | Crainosacral portion of the spinal cord | Acetylcholine | Cholinergic neurons<br>1-Preganglionic N. release Ach into nicotinic R. OF postganglionic N.<br>2-postgangilonic N. release Ach into the effectors tissue | M1-M5<br>Nn<br>Nm |

**Neurotransmitter** : Is a chemical substance transmit impulse across junctions such as synapse

## The adrenergic receptors:

| α 1 | α 2 | β 1 | β 2 | β 3 |
|---|---|---|---|---|
| 1- Found in the blood vessels :vasoconstriction<br>2- Uterus: contraction<br>3- Eye : contraction of radial M. leading to mydraisis<br>4- GIT and bladder : Wall → relaxation Sphincters → contraction<br>5- Sweat gland of palm and forehead : increase sweating<br>6- Salivary gland :↑ salivation | 90% of these receptor found presynaptically in the brain : decrease NE release | Found in the heart : increase heart rate leading to tachycardia | 1- Lung :bronchodilation<br>2- Blood vessels of skeletal muscle :vasodilation<br>3- Coronary artery : vasodilation<br>4- Liver : ↑ glycogenolysis → ↑glucose in blood<br>5- Make the N. receptor more sensitive to Ach<br>6- ↑ the intracellular K → hypokalimaia | Found in adipose tissue → lipolysis |

## Notes :

1- Most organs are innervated by both division of the ANS (dual innervation )

2- Some organs are supplied by one division - Iris sphincter M. (circular M.) : supply by parasympathetic M3 receptors - Iris dilator M. (radial M.): supply by sympathetic α 1receptors - Pilomotor M. : supply by sympathetic α 1receptors ( hair erection )

3- Thermoregulatory sweat gland : supply by sympathetic fiber but through M3 receptors

4- Adrenal medulla : supply by sympathetic fiber through nicotinic receptors

5- Blood vessels : are innervated by sympathetic indirect non – innervated by parasympathetic - Direct acting : innervated by sympathetic α 1 receptors → vasoconstriction - Indirect acting: non innervated parasympathetic M3 receptors → vasodilation via the nitric oxide .

**Enteric nervous system (NANC nerve)**

Is the division of the nervous system which innervated the intestine (local control system ) , the co-transmitter (ATP ,purins,histamine , serotonin and nitric oxide ) responsible for the activity of these system .

**The comparison between sympathetic and parasympathetic system according to their pharmacological effects:**

| Sympathetic | Parasympathetic |
|---|---|
| Tachycardia | Bradycardia |
| Vasoconstriction | Vasodilation |
| ↑ BP | ↓BP |
| ↓ renal blood flow | ↑ renal blood flow |
| ↓ urine out put | ↑ urine out put |
| Brochodilation | Brochconstrction |
| ↓GIT motility and secretion | ↑GIT motility and secretion |

**Adrenergic agonist (sympathomimetic)**

**These drugs can be classified according to their mode of action :**

1-direct acting :drugs that acting directly on the adrenergic receptors

2-indirect acting :drugs that release NE from the nerve ending .

3- MAO inhibitors : drugs that destroy the monoamino oxidase enzyme thus prolong the action of catecholamine

**Also can be classified these drug according to their chemistry into :**

**1- <u>Catecholamine</u>**

Dopamine

Norepinephrine

Epinephrine

It's have essential properties :

1-not absorbed orally ,

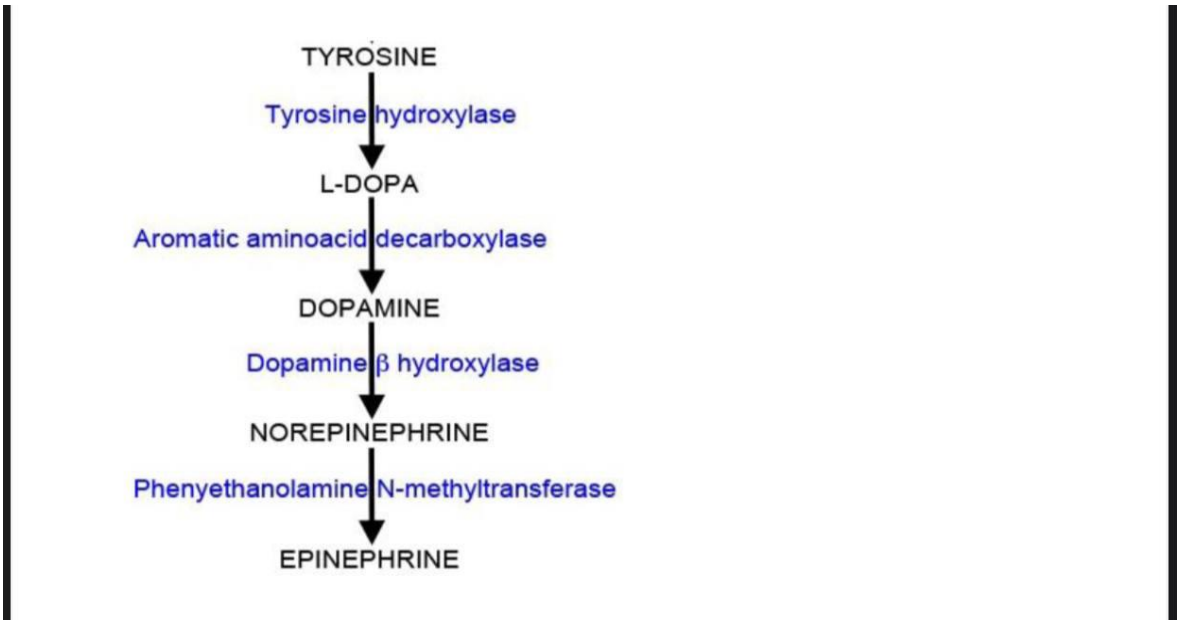
2-not cross BBB,

3-inhibited by MAO and COMT ,

4-short acting

## Catecholamine :

Biosynthesis




**Epinephrine (adrenaline )**

Discovered in 1895 in suprarenal gland Synthsis in 1904

1-chemistry

2-pharmacokinetic

3-pharmacodynamic (mechanism of action )

4-uses

5-adminstration

6-adverse effect

7-Contraindication

1- Chemistry of adrenaline : adrenaline is natural in the body and contain catecholamine ring .
2- Pharmacokinetic :

**Absorption : -**

– Not absorb orally

– In the skin cause vasoconstriction

– Eye :very low absorption because the tear contain MAO

–Can absorb well by inhalation

**Distribution**

Reach all the body except brain , brain have adrenaline but injectable adrenaline can not cross the BBB.

**Metabolism**

**1-Tissue uptake mechanism** : remove the drug from the receptor site thereby decreasing the NO. of receptor being occupied and decrease the response

Uptake 1: is the uptake the drug from the receptor into the presynaptic neurons. coccaine produce sympathomimetic effect by blocking uptake 1.

Uptake 2: is the uptake of catecholamine into the effector cell which contain :

**MAO –MONOAMONOOXIDASE**

**COMT –catechol-o-methyl transferase**

These 2 enzyme metabolize catecholamine into inactive product Metanephrine and vaniline mandilic acid VMA which can be detected in the plasma and urine , these end product increased in :

1.stress

2.adrenaline injected

3.pheochromocytoma .

**Note :**80% of adrenaline into the vesicles by uptake 1 and uptake 2 20% of adrenaline is metabolized by COMT in the nerve space and MAO inside the nerve terminals

**II. The liver and kidney which are rich in MAO and COMT inactivate circulating catecholamine**

**Administration:**

S/C

IV……RISK ……dangerous arrhythmia

IM

**Mechanism of action**

Is potent agonist of α 1, α 2, β 1, β 2 and β 3.

**Pharmacological effects**

Heart : tachycardia → β 1

Blood pressure: ↑BP→ α 1

Lung :bronchodilation → β 2

CNS : X

EYE : mydriasis →↓IOP

Uterus : contraction → α 1

Relaxation → β 2

Depending on the state of estrus cycle , pregnancy and species

Liver :↑glycogenolysis

Spleen : contraction → α 1 leading to ↑RBC in dogs .

Pilomotor muscles : contraction → α 1.

**Uses**

1- Anaphylactic shock IM.

2- Acute bronchial asthma S.C,IM or inhalation

3- Cardiac arrest

4- Prolong the effect of local anesthetic .

5- Treatment of the open angle glaucoma

**Adverse effects**

1- ↑BP and cerebral hemorrhage

2- Tremors

3- Tachycardia

4- Acute heart failure

5- Acute pulmonary edema

6- Gangrene of fingers

**Contraindication**

1. Hypertensive patient

2. Cardiovascular problem

3. Large dose of local anesthetic

4. Cardiac outflow obstruction

5. Hyperthyroidism

## Noradrenaline

**Mechanism of action**: its potent agonist on α 1, α 2 and β 1 receptors

90% on α 1----------10% on β 1

**Uses** : acute hypotension

**Administration :** not SC or IM or IV but only intravenous infusion because of tissue necrosis .

**Dopamine :**

Dopamine receptors:

D1→ Renal, mesenteric and coronary circulation → vasodilation

D2→CNS

D3→CNS

D4→Heart and CNS

D5→LYMPHOCYTE

**MECHANISM OF ACTION**

Low dose →activate D1 →Vasodilation

Intermediate dose →activate β 1→ increase cardiac output

Large dose → activate α 1 →vasoconstriction

**Uses**

Shock state with impaired tissue perfusion

**Administration**

IVI only

**Beta agonist**

1- Selective beta 2 agonist

2- Selective beta 1 agonist →dobutamine

3- Non selective beta agonist →isoprenaline Its synthetic cat act on β1 and β 2

**Selective β 2 agonist** -Salbutamol -Retordine -Terbutaline -Salmetrol -zilpaterol

 Its non-catecholamine

 Taken orally

 Have long duration

 Not destroyed by MAO and COMT

**USES**

1-bronchial asthma

2- uterine relaxation (retodrine )

**Adverts effects**

T→Tachycardia

T→ Tremors

T→Tolerance

H→ Hypokalemia

**Alpha agonist**

**α 1 agonist**

phenylpherine , methoxamine (non cat)

act as vasopressor

**administration**

1.injectabel

2.eye drop

3.nasal drop

4. tablet

Uses

1. Red eye

2. Nasal decongestion

**Adverse effect :**

1.rebound congestion

2.strok hypertension

3. atrophic rhinitis .

**Alpha 2 agonist**

Xylazine , medotimidine , detomidine , clonidine , tizanidine

**Chemistry :** its non cat

**Mechanism of action :**

Agonist on α 2 receptors which decrease the secretion of adrenaline peripherally and

centrally because the drug is not cat .

**Clinical uses**

1- Sedation

2- Anesthesia

3- Muscle relaxation

4- Analgesia

5- Emetic in cat

6- Hypertension

7- Treat withdrawal syndrome

**Adverse effect**

S→ Sedation , dry mouth

S→ Sudden withdrawal lead to sever hypertension

S→ Salt and water retention

**Tizanidine** :act specially on the α 2 receptor in the spinal cord leading to muscle relaxation so it used in muscle spasm .

**Indirect sympathomimetic**

Can be divided into

-indirect

-mixed acting

**1- indirect acting**

**- Amphetamine** : its synthetic drug , not catecholamine ,absorbed orally Act on the nerve ending promote adrenaline release and inhibit the uptake leading to accumulation of NE,E,D and serotonin in the synaptic space

**Effects**

- CNS stimulation
- Anorexia
- Euphoria
- Hallucination

**Adverse effect :**

- -physical dependence
- insomnia
- -nervousness
- -headache
- -Seizure

**Notes :**

Amphetamine derivatives→ methylphenidate uses in attention deficit – hyperactivity

syndrome

**modafinil:** used in narcolepsy

**cocaine :** its plant alkaloids inhibit reuptake of E used as local anesthetic

toxicity of cocaine treated by benzodiazepame

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**2- mixed acting sympathomimetic**

**Ephedrine**: act on the α and β receptor and stimulate the release of adrenaline from the

nerve ending

**Chemistry :** its natural from plant alkaloid , its non cat

**Effects**: CNS stimulation

**Pseudoephedrine** : available as eye drop and nasal drop to treat congestion

**Notes :** ephedrine cause urinary retention because it stimulate α 1and β 1 receptor inthe bladder and contraction of the sphincter and because it have long duration of action (8h) unlike adrenaline which is catecholamine remain in the body for few min.

**adrenergic blockers**

**Alpha adrenergic blocker** :

- α 1 and α 2 nonselective blocker (phenoxybenzamine , phentolamine )
- selective α 1 blocker prazosin
- selective α 2 blocker yohimbine

 ergot alkaloids

non selective α 1 and α 2 blocker:

**phenoxybenzamine :**

its blocker to α receptors , its bind to receptors irreversibly by covalent bond .

long acting 4days

**uses**

1- In pheochromocytoma with propranolol (which block β 1 and β 2).

2- In dog and cat reduce hypertonus at urethral sphincters

3- In horse: treat laminitis and secretory diarrhea.

**Adverse effect :**

1- ↓BP with reflex tachycardia.

2- Failure of ejaculation.

3- Miosis

4- Not use in horse with colic

**Phentolamine**

It's a competitive α 1 and α 2 receptors antagonist .

**selective α 1 blocker:**

**prazosin**

its act by block α 1 receptors

**effects**

1-vasodilation

2- direct relaxation of smooth muscle of blood vessels

3- Don't affect RBF

5- ↓BP and lipid profile (cholesterol and triglyceride )

**Uses :**

1- Hypertensive patient with renal disease

2- Acute heart failure

3- Urine retention in benign prostate hypertrophy

**Adverse effect :**

F→ First dose syncope

F→ Fluid retention

U→ Urine incontinence

**Selective α 2 blocker**

**Yohimbine**

Is competitive α 2 receptors antagonist .

**Pharmacological effects:**

1- CNS stimulation

2- ↑ BP by increasing parasympathetic tone

3- ↑ HR

**Adiminstration : IV and IM .**

**USES :** reverse the effect of α 2 agonist .

**Beta blocker**

1- β 1 and β 2 blockers :propranolol , nadolol, satolol and timolol

2- β 1 blockers: atenolol , esmolol ,metoprolol

3- β 1 blocker with direct vasodilator : carvedilol and labetalol

**Beta blocker with special effect**

1- Propranolol: membrane stabilization action so it have local anesthetic effect and antiarrhythmic action .

2- Pindolol: partial agonist---no brady cardia

3- Esmolol: very short acting use during surgery to prevent arrhythmia .

4- Labetalol: beta and alpha 1 blocker ----pheochromocytoma .

5- Carvidolol : antioxidant action .

**Uses :**

1- Hypertensive patient .

2- Ischemic heart disease .

3- Supraventricular arrhythmia

4- Hyperthyroidism

5- Glaucoma (betaxolol)

6- Pheochromocytoma .(timolol).

**Adverse effects:**

1- Fatigue due to ↓COP and ↓ blood supply of skeletal muscle

2- Bronchoconstriction .

3- Bradycardia

4- Peripheral ischemia.

**Adrenergic neuron blocker**

**α - methyldopa**

**mechanism of action** :

its act by enter in the NE synthesis as a false substrate which result in α - methylnorepinephrine (false transmitter ) which act on α 2 receptor .

**uses :** treatment hypertensive pregnant

**clonidine**

**reserpine**

**mechanism of action :**

this drug facilitate the NE release from the nerve ending and prevent reuptake 2 to thevesicle which result in destroyed by MAO leading to depletion of NE , D and 5HT .

**Direct acting parasympathomometic**:

1- Carbachol : its agonist on M and N receptors , have resistance to ChE so its have long duration of action 2-3h .

Use as eye drop to treat glaucoma .

2- Bethanecol : its agonist on M receptors only , have resistance to ChE.

**Uses :**

1- SC to treat the distention of the U.B.

2- SC to treat GIT and uterine atony .

**Precaution :**

1- oraganic obstruction .

2- bronchial asthma . ----------

3- Pilocarpine : agonist on M and N receptors used in glaucoma .

**Side effects**

D→ diarrhea ,

U→ uresis

M→ miosis

L→ lacrimation

E→ emesis . excitation of CNS

S→ Salivation

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**Indirect parasympathomimetic**

- Reversible

- Indirect parasympathomimetic ( carbamylation )

- Irreversible - Indirect parasympathomimetic ( phosphorylation )→ organophosphorus compound .

- Reversible - Indirect parasympathomimetic ( carbamylation )

This group of drug inhibit the ChE enzyme by carbamylation .

1- Physostigmine

2- Neostigmine

3- Pyredostigmine

4- Edrophonium .

**Note :**

1- in case of poisoning with physostigmine use atropine as antidote

2- Neostigmine have 2 mechanism to treat myasthenia gravis - ChE inhibitor →↑Ach - Direct acting on NMJ →Nm receptor .

3- Neostigmine +atropine to treat block M receptors .

4- Edrophonium : more selective on NMJ but have short duration of action so it uses for diagnosis myasthenia gravis .

5- Pyredostigmine more selective on NMJ , not need atropine to block M receptors .

**Irreversible - Indirect parasympathomimetic ( phosphorylation )→**

**organophosphorus compound .**

1- Insecticide , malathion , parathion .

2- Ecothiophate

3- Nerve gases ---- sarin and soman

- These compound have very rapid of absorption (skin , orally and inhalation )

- These compound make covalent bond with the enzyme

- Complete inhibition occur in 12 h.

- 3h 50% of enzyme inhibited …….aging of the enzyme .

**Muscle relaxant :**

**Classification**

1- Agent acting on NMJ -competitive non- depolarizing agents : curare - depolarizing agent: succinylcholine .

2- centrally acting M relaxant :xylazine , diazepam .

3- local anesthesia as lidocaine .

4- direct acting M relaxant as dantroline.

**competitive non- depolarizing agents**

agent antagonize N receptors at NMJ causing muscle relaxation . - Tubocurarine - Aminoglycosides - Pancuranium - Gallamine

**depolarizing agent**

succinylecholine (Ach-ch)

agent depolarizing muscle membrane after stimulation of N receptors causing muscle relaxation .

**note**

1- metabolize by pseudocholiesterase in plasma and liver .

2- has short duration of action in horses because high level of pseudocholiesterase

3- dangerous in ruminant because of low level of pseudocholiesterase .

4- ChE inhibitors potentiate the action of succinylecholine .

5- not cross BBB.

6- It ↑HR and BP because the release of adrenaline.

# Drugs acting on the Central Nervous System (CNS)

The CNS is consisted of the brain and spinal cord. The brain composed of the cerebrum, cerebellum and medulla oblongata.

## Neurotransmitters

Neurotransmitters are biological substances that transmit signals from a presynaptic neuron to a target receptor on the postsynaptic neuron.

## Types of neurotransmitters in the CNS:

1. Acetylcholine (Ach).

2. Catecholamines that composed of Norepinephrine (NE), Epinephrine (Epi) and Dopamine (DA).

3. Serotonin (5-hydroxy tryptamine)(5-HT).

4. Aminoacids that divided into:

A. Inhibitory (GABA and Glycine).

B. Excitatory (Aspartate and Glutamate).

## Sedatives and Hypnotics

Hypnotics are drugs that cause hypnosis by depressing the CNS so the animal is less responsive to external stimuli. Hypnotics that used in small doses will cause sedation.

### Types

### Barbiturates

Divided into:

A. Long acting (Phenobarbital). B. Short acting (Pentobarbital).

C. Ultra-short acting (Thiopental).

## Mechanism of action

Potentiate the effect of GABA neurotransmitter leading to depression of the brain and inhibits excessive motor discharge.

## Pharmacological effects

1. Depresses all functions of the brain.

2. Selectively depresses the motor cortex.

3. Depresses the respiratory center in medulla.

4. Produce good muscle relaxation.

5. Decreases blood pressure and heart rate.

6. Induce microsomal enzymes and increase the metabolic rate of the animal.

## Clinical uses

1. Sedative.

2. Hypnotic.

3. Anticonvulsant.

4. Anesthetics.

5. In case of pruritus to control itching.

## Benzodiazepines

Which include diazepam, chlordiazepoxide and alprazolam.

## Mechanism of action

Increasing the action of GABA neurotransmitter on its receptor which causes influx of chloride ion into the neuronal cells leading to depression of the CNS.

## Clinical uses

1. Sedative.

2. Hypnotic.

3. Muscle relaxant.

4. Anticonvulsant.

5. Preanesthetic.

6. Antianxiety.

## Chloralhydrate

It is hypnotic given I.V. in large animals (7%). It depresses the respiratory and vasomotor centers. It is metabolized in the body by reduction into Trichloroethanol which is the active metabolite responsible of hypnotic effect of chloral hydrate. It is used as anesthetic in equine species with weak analgesic effect and can be mixed with Magnesium sulfate ($MgSO_4$) (6%) to produce muscle relaxation. Chloral hydrate decreases blood pressure and decreases heart rate and sudden death may occur in horses which are highly excited.

## Ethanol

It has sedative effect, depresses respiration and causes vasodilation. It has diuretic effect because it inhibits antidiuretic hormone (ADH). It metabolized into $CO_2$ and $H_2O$ and small amount expired by the lungs.

## Anticonvulsant Drugs

Are drugs used to control seizure through depressing the CNS.

## Types

Barbiturates

Benzodiazepines

Phenytoin

## Mechanism of action

It stabilizes the neuronal membranes and selectively depresses the motor areas in the brain.

It is not hypnotic, well absorbed orally, induces liver microsomal enzymes, metabolized in the liver and excreted in the bile.

## Side effects

1. Transient incoordination.

2. Polyphagia.

3. Polyurea.

## Primidone

The structure of this drug and its mechanism of action is similar to phenobarbital and about 25 % of the drug is metabolized into phenobarbital. It causes nausea, ataxia and not used in cats because it causes neurotoxicity.

## Morphine

## Mechanism of action

It acts on opioid receptor (Mu receptor) in the CNS leading to depression of the brain and causing analgesia.

## Pharmacological effects

### A. On the brain:

Depresses the brain in dogs, monkey and human but it causes CNS excitation in cats, horses and ruminants.

### B. On the GIT:

The initial dose of morphine causes defecation but chronic use causes constipation.

### C. On the skin:

Morphine causes itching because of histamine release.

## Clinical uses

1. Analgesic.

2. Preanesthetic.

## Toxicity

Death may result from respiratory depression and it can be treated by giving opioid receptor antagonist like Naloxone.

# Tranquilizers

Are drugs used to tranquilize and control of the animals and they are called also **Neuroleptics**.

### Types

### Chlorpromazine, Acepromazine and Promazine.

### Chlorpromazine

### Mechanism of action

They antagonize dopamine receptors in the brain leading to depression of the CNS. It also has anticholinergic and antiadrenergic effects.

## Clinical uses

1. Control the nervous animals.

2. Preanesthetic.

3. Antipruritus.

4. Antiemetic.

5. Antistress in transporting of animals.

## Side effects

1. Incoordination in horses. 2. Dry mouth.

3. Constipation.

4. Hypotenstion.

5. Decreases body temperature.

# CNS Stimulants

## Types

## Caffeine, Theophylline and Aminophlline.

## Mechanism of action

Antagonism of adenosine receptors in the brain leading to CNS stimulation.

## Pharmacological effects

1. Stimulates CNS, decrease fatigue and increases motor activity.

2. Stimulate the heart and causes vasodilation.

3. Relaxation of smooth muscle therefore theophylline is used in asthma. 4. Diuretic effect through increasing renal blood flow.

5. Stimulation of gastric acid secretion.

## Amphetamine

## Mechanism of action

It increases the release of Norepinephrine and Dopamine from the nerve endings leading to CNS stimulation.

# Medullary Stimulants

## Doxapram

### Mechanism of action

It stimulates the respiratory center in the medulla and causes respiratory stimulation.

#### Clinical uses

1. Antagonizes the respiratory depressant action of Barbiturates.

2. Antagonizes the sedative action of xylazine.

## Nikethamide

It is a short acting respiratory stimulant.

# Spinal Cord Stimulants

## Strychnine

### Mechanism of action

Antagonizes glycine receptors in the spinal cord.

#### Indications

1. Improves appetite in very small quantity.

2. Used as tonic.

3. Kill the stray dogs.

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Department of optical techniques
Lecturer: MSc..Mais aldouri

# Cardiovascular Drugs

## Syllabus

1• Haematinics.

2• Cardiotonics.

3• Anti anginals.

4• Antihypertensives .

5• Anti – arrhythmic.

6• Anticoagulants.

7• thrombolytics.

8• Hypolipidemics.

## 1-Haematinics:

•Haematinics are the drugs which used to stimulate the formation of RBC's These are used primarily in the treatment of Anemia. Eg. Iron.

## Mechanism of action:

•They act as supplement and replace depleted iron stores in the bone marrow to assist in the erythropoiesis (RBC production).

## 2-Cardiotonics:

•These are the drugs which have a positive inotropic effect on heart. They increase the force of myocardial contraction without corresponding increase in O2 consumption. They are used for the treatment of congestive heart failure.

## Mechanism of Action :

•Cardiac glycosides inhibit the enzyme Na-K-ATPase present in cardiac muscle. This cause an increase intracellular Na & Ca in heart muscle cells that leads to increase in force of contraction.

## 3-Anti anginals :

• Angina pectoris is the chest pain due to anoxia of heart muscles generally due to obstruction or spasm in coronary artery. The drugs used in angina pectoris prevent terminate attacks of angina pectoris are called antianginal drugs.

• These drugs are mainly classified as:

1. Nitrates.

2. Beta - Blockers. (already described)

3. Calcium channel blockers. (already described)

**Nitrates**

•Nitrates are the drugs which are vasodilator effects thus used in angina pectoris.

**Mechanism of action**

•Nitrates release NO (Free radical nitric oxide) which is powerful muscle relaxant. So they produce vasodilation, decreased preload and afterload, reduce myocardial oxygen consumption.

## 4-Antihypertensives:

•Hypertension is a disease characterized by abnormally high blood pressure.

## 5-Anti-arrhythmics :

• Arrhythmias means abnormal cardiac rhythm. It occur due to an abnormal excitability of a part of cardiac muscle or due to an abnormality in conduction system of heart. So these drugs are used for arrhythmia.

## Mechanism of action:

• These drugs block Na+ (Sodium) channel of cell membranes and reduces excitability of cardiac muscle and slows the conduction in heart.

## 6-Anticoagulants:

• These are the agents which inhibit the process of clotting, thus they are used to prevent unwanted thrombosis.

## 7-Thrombolytics :

• These drugs are used to lyse (Dissolve) thrombus or clot.

## Mechanism of action:

• These agents activate plasminogen to form plasmin thus dissolve clot or thrombosis. (Plasminogen Plasma Clot dissolution).

## 8-Hypolipidemics:

• These drugs are used in the treatment of atherosclerosis and hyperlipidemia.

## Mechanism of action:

• They inhibit the synthesis of cholesterol in liver also they inhibit the transfer of triglycerides from liver to plasma and block HMG- COA reductase in the liver preventing cholesterol synthesis.

# Drugs Affecting the Endocrine System

# And

# Chemotherapeutic Drugs I , II

**MSC.. MAIS ALDOURI**

* تقرير عن علاج كيميادي بمصادر حرية
كروب 5 طلاب
او كل طالب عن نوع دواء واحد

# Drugs Affecting the Endocrine System

## Objectives:

1. How body functions are controlled & maintained
2. Mechanism of action of hormones
3. Drugs used for hormonal replacement therapy
4. Indications of hormonal analogs (hormone agonists & antagonists)

**References**: Lippincott (Illustrated Reviews Pharmacology), Internet

- An important function of the hypothalamus is to connect the nervous system with the endocrine system via the pituitary gland. roendocrin tar
- Pituitary & hypothalamus control the system transmitting messages between individual cells & by
- Nervous system communicates locally by electrical impulses & neurotransmitters. Nerve impulses generally act within milliseconds.
- The endocrine system releases hormones (chemical messengers) into the blood stream, from which they reach their target cells.
- Response time to hormones may be seconds - days, or longer.

**Note:** response to hormones may last for weeks or months.

- In several instances, the release of hormones is stimulated or inhibited by the nervous system, & some hormones (Hs) can stimulate or inhibit nerve impulses.

## Hypothalamic & anterior pituitary hormones

-Peptides or low-molecular-weight proteins.

-Bind to specific receptor sites.

-Hypothalamus produce releasing or inhibiting factors (or Hs), which regulate the anterior pituitary (AP) Hs.

**Note:** hypothalamic-releasing hormones (RHs) are primarily used for diagnostic purposes, e.g. CRH is used to differentiate between Cushing syndrome & ectopic ACTH-producing cells.

## Anterior pituitary hormones:

### Adrenocorticotropic hormone (ACTH) or Corticotropin

ACTH synthesized & released from the AP under the -influence of CRH.

-ACTH is released in pulses with a diurnal rhythm, highest concentration occurring at 6 AM & lowest in the late evening.

-Stress stimulates ACTH secretion, whereas cortisol suppresses it (via negative feedback).

### Mechanism of action:

Binding of ACTH to its receptors → activate G protein → ↑ CAMP conversion of cholesterol to pregnenolone (a rate limiting step in the adrenocorticosteroid synthesis) → synthesis & release of adrenocorticosteroids & adrenal androgens.

### uses

1. To differentiate between primary adrenal insufficiency (Addison disease) & secondary adrenal insufficiency.
2. Infantile spasm (West syndrome) treatment.

### Growth hormone (GH) or Somatotropin

-Large polypeptide released by the AP.

Somatostatin (from hypothalamus), inhibits GH -secretion.

-Highest levels of GH is released during sleep.

-With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass.

Somatropin is a human GH synthesized by -recombinant DNA technology,

administered as SC or IM injection, (note: GH from animal sources is ineffective). Although the half-life of GH is short (about 25 minutes), it induces release of IGF-1 from the liver, which is responsible for subsequent GH-like actions.

**Mechanism of action:**

Many physiologic effects of GH are exerted directly at its targets, others are mediated by somatomedins-insulin-like growth factors I & II (IGF-I and IGF-II) (note: In acromegaly, IGF-I levels are high, reflecting elevated GH).

**Uses:**

(1) GH deficiency in children (dwarfism).
(2) management of AIDS wasting syndrome
(3) GH deficiency in adults with confirmed deficiency to increases lean body mass, bone density, and skin thickness, whereas adipose tissue is decreased.

**Somatostatin (GH-inhibiting hormone)** →

-Suppress GH & TSH release.
-It also found in neurons, intestine & pancreas.
It also inhibits release of, insulin, glucagons & -gastrin.

**Octreotide** and **Lanreotide** → synthetic **somatostatin** analogs with longer half- life (they are given as depot formulations once every 4 weeks), used to treat acromegaly, diarrhea and flushing associated with carcinoid tumors.
**Octreotide** IV infusion → used to treat bleeding of esophageal varices.
**Octreotide** adverse effects → flatulence, diarrhea, nausea & steatorrhea.
Gallbladder emptying is delayed & long-term therapy may cause asymptomatic cholesterol gallstones.
**Pegvisomant** → GH receptor blocker used to treat acromegaly that is refractory to surgical, radiologic, or pharmacologic intervention.

**Gonadotropins - releasing hormone (GnRH)** → هرمون غدد تناسلية

-Its pulsatile secretion is essential for gonadotropins (FSH & LH) release.

-GnRH analogs are used to treat prostatic cancer, endometriosis & precocious puberty. → علاج سرطان بروستات وبطانة الرحم والبلوغ المبكر

- Leuprolide is also used to suppress the LH surge and prevent premature ovulation in women undergoing controlled ovarian stimulation protocols for the treatment of infertility. [Note: GnRH antagonists such as cetrorelix and ganirelix can also be used to inhibit LH secretion in infertility protocols.]

-In women GnRH analogs may cause hot flushes, sweating & diminished libido, depression & ovarian cysts.

-Contraindication → pregnancy & lactation.

-In men, they initially cause a rise in testosterone that can result in bone pain, hot flushes, edema, gynecomastia & diminished libido.

**Gonadotropins:**

FSH & LH are glycoproteins that are produced in the -AP. → بروتينا = سكريات

-Regulate gonadal steroid hormones secretion. → تنظم افراز الهرمونات = المستويدية للغدد التناسلية

-Used to treat infertility in men and women. → وتستخدم لعلاج العقم

**Menotropins** (Human menopausal gonadotropins "hMG"): Obtained from the urine of postmenopausal women, it contain both FSH & LH.

**Urofollitropin**: FSH obtained from postmenopausal women.

**Human chorionic gonadotropin (hCG):** Placental hormone, excreted in the urine. → هرمون غدد تناسلية المشيمة

- hCG and choriogonadotropin alfa (made by recombinant DNA technology) are identical to LH.

- hMG or FSH injected over a period of 5 to 12 days causes ovarian follicular growth & maturation, then subsequent injection of hCG induce ovulation. → يحفز الإباضة

-In females adverse effects → ovarian enlargement &

possible ovarian hyperstimulation syndrome (may be life threatening) & multiple births.

**Prolactin (PRL) :**

- Peptide hormone secreted by the AP.
- Dopamine (at D2 receptors) inhibit PRL secretion [Note: dopamine antagonists e.g. metoclopramide & antipsychotics like risperidone increase PRL secretion].
- PRL decreases sexual drive & reproductive function.
- D2 receptor agonists eg. bromocriptine & cabergoline are used to treat hyperprolactinemia (galactorrhea & hypogonadism) & microadenomas, bromocriptine is also indicated to treat type 2 DM.
- Their adverse effects nausea, headache & psychiatric problems.

**Posterior pituitary hormones**

- **Vasopressin & oxytocin,** they are not regulated by RHs. RHS
- Synthesized in the hypothalamus, transported to the posterior pituitary & released in response to high plasma osmolarity or parturition.
- Both Hs are susceptible to proteolytic cleavage.
- Given IV & have very short half-lives.

ملاحظة / هاي الملازمة دكتورة كالت راح تسوي 5 اسئلة عنها وتدزها

# Chemotherapeutic Drugs I , II

## INTRODUCTION

Cancer therapy has improved substantially over the past decade. As a result, patients in increased numbers are now treated with successive chemotherapy lines with a significantly increased survival. Over 200 chemotherapeutic agents are now available. Most anesthetists encounter patients receiving anti-cancer chemotherapies on a regular basis and they need a working knowledge of these drugs in order to optimize patient safety. Entire textbooks could be written on this topic. The purpose of this talk is merely to provide an approach.

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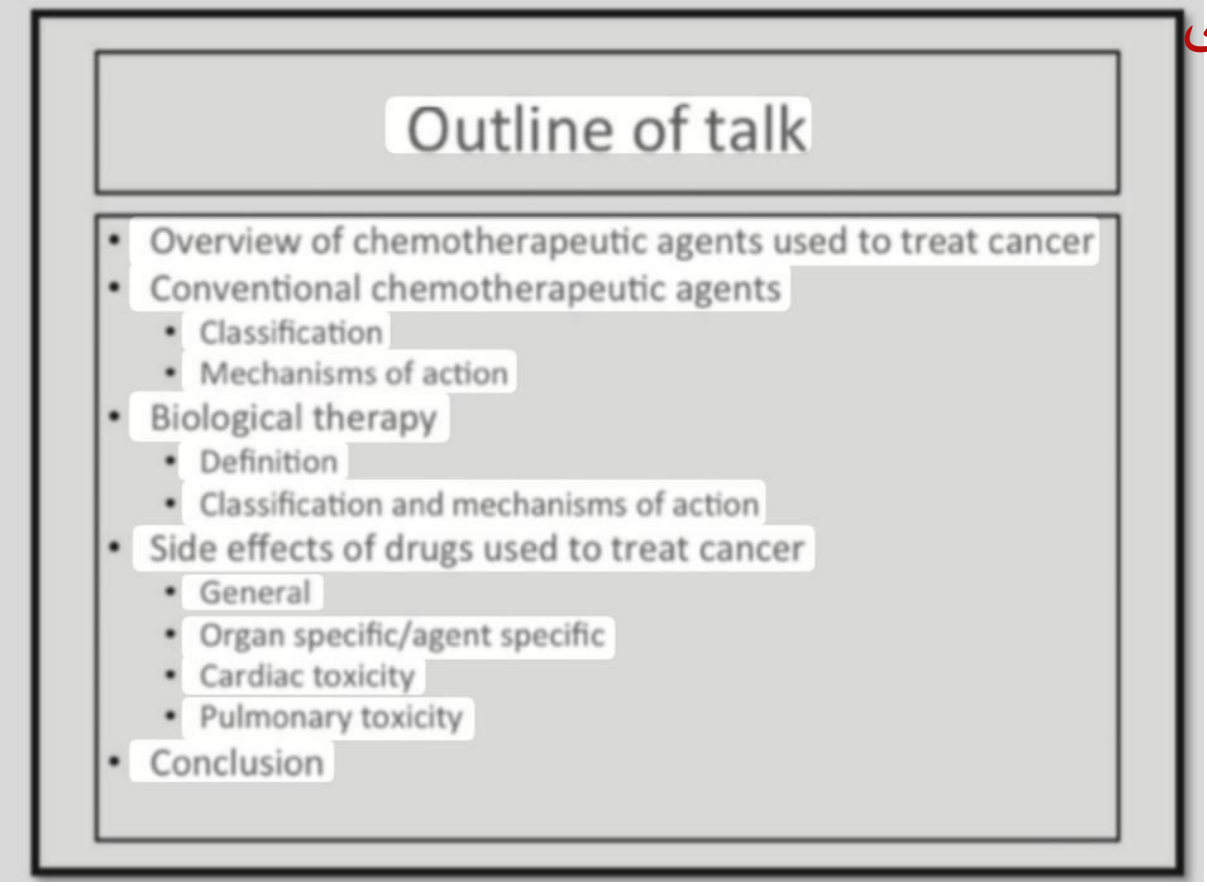

# CONVENTIONAL CHEMOTHERAPEUTIC AGENTS

Traditional chemotherapeutic agents are cytotoxic i.e. they act by killing cells that divide rapidly, one of the main properties of most cancer cells. This means that chemotherapy also harms cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract and hair follicles.

## BIOLOGICAL THERAPY

Biological therapy involves the use of living organisms, substances derived from living organisms or laboratory-produced versions of such substances to treat disease. Biological therapies that interfere with specific molecules involved in tumor growth and progression are referred to as targeted cancer therapies as they target cancer cells directly. Some types of biological therapy exploit the immune system's natural ability to detect and kill cancer cells. These are referred to collectively as "immunotherapy"

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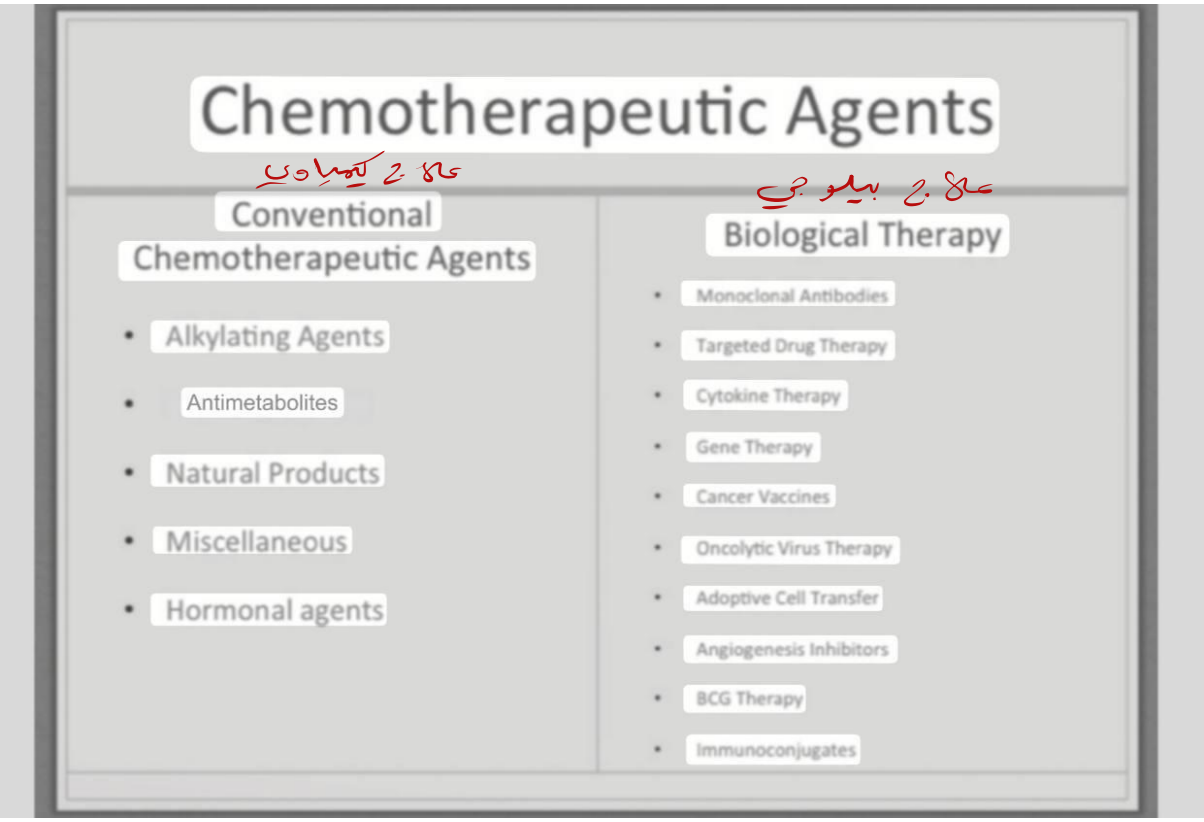
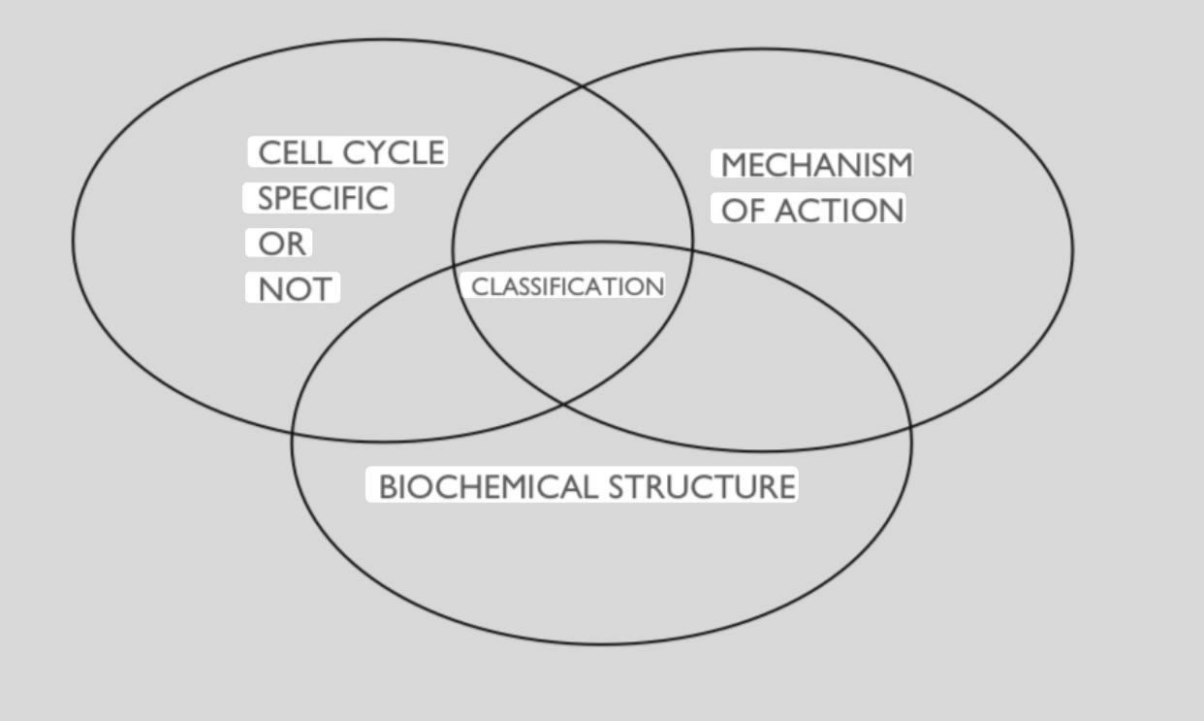


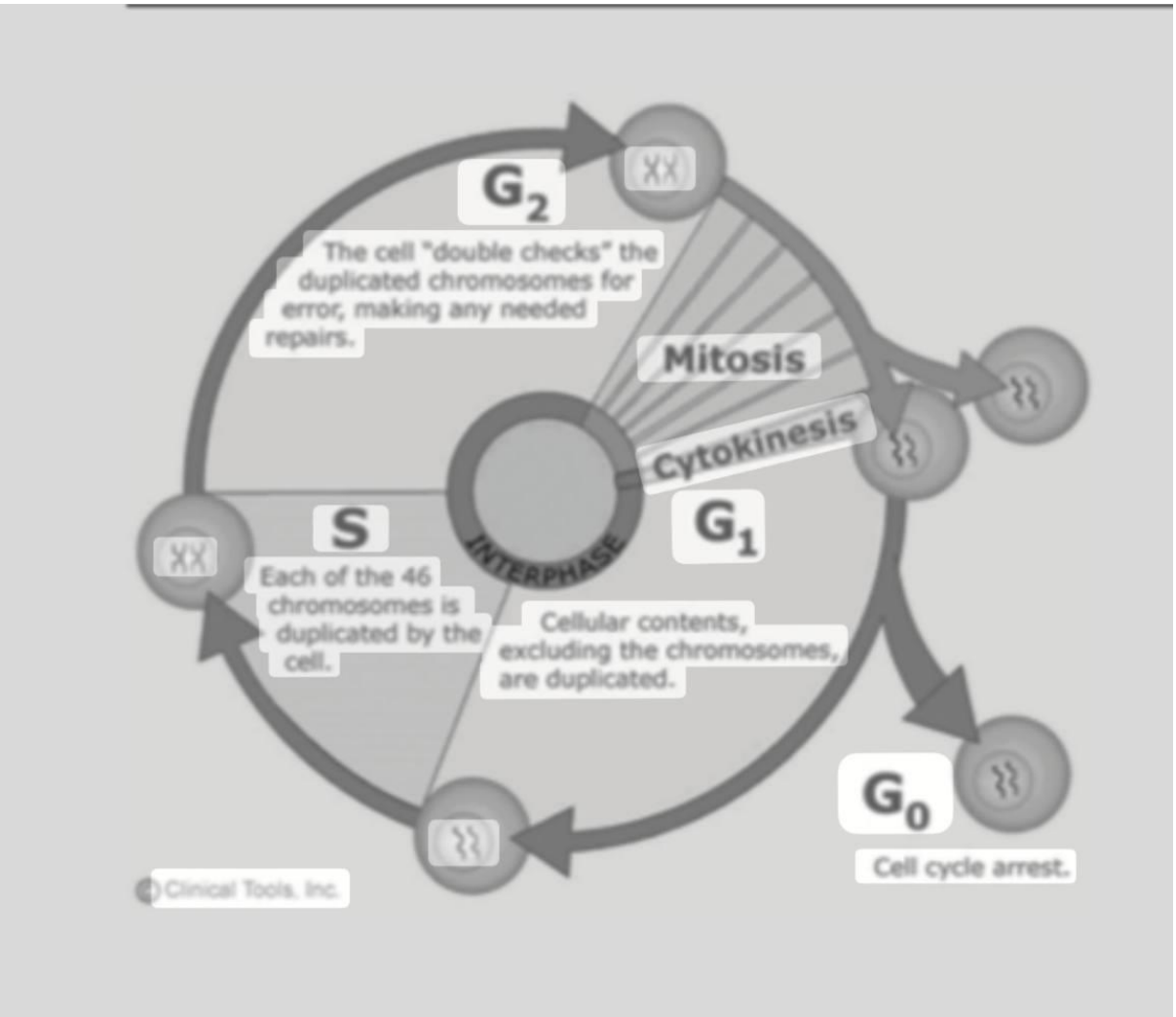
**CLASSIFICATION AND MECHANISMS OF ACTION OF THE CONVENTIONAL CHEMOTHERAPEUTIC AGENTS**

In the broad sense, most conventional chemotherapeutic drugs work by impairing mitosis(cell division), effectively targeting fast-dividing cells. As these drugs cause damage to cells they are termed cytotoxic. They prevent mitosis by various mechanisms including damaging DNA and inhibition of the cellular machinery involved in cell division.
Besides being classified as cell-cycle specific or non-specific, cytotoxic agents are also classi- fied based on their biochemical structure and mechanism of action. Because some drugs act in more than one way, they may belong in more than one group.




**PHASES OF THE CELL LIFE CYCLE**
The cell "double checks" the duplicated chromosomes for error, making any needed repairs.
The life cycle of eukaryotic cells comprises numerous phases.
Chemotherapeutic drugs can be classified as either phase-specific or non-phase-specific drugs. A phase-specific agent is only effective during a specific

phase of the cell life cycle, whereas a non-phase-specific agent is effective during all phases.




**Go phase**: Gap / resting state where cell is not dividing.

**GI phase:** Gap I/interphase
Phase for the production of specialized proteins, RNA, enzymes for DNA synthesis.
**S phase**: DNA synthesis. Phase for doubling cellular DNA
**G2 phase**: production of cellular components for mitosis: DNA, RNA, micro tubular pre- cursors of mitotic spindles.
**M phase:** Mitotic phase: cells divide: RNA production followed by cell duplication.

**NON-PHASE SPECIFIC DRUGS**

These drugs kill dividing cells at any point in the life cycle. They are effective for both low and high growth fraction malignancies. They demonstrate a linear dose-response curve implying improved cell death with increased dose. Examples of these agents include: Platinum compounds, alkylators, nitrosoureas, steroid hor- mones and anti-tumor antibiotics (except bleomycin).

**PHASE SPECIFIC DRUGS**

Cell life cycle phases targeted by chemotherapeutic drugs

| Phase | Examples |
|---|---|
| Go phase | Relatively drug resistant phase |
| GI phase | Anti-tumor antibiotics<br>Nitrosoureas<br>Cisplatin<br>L-asparaginase<br>Dacarbazide |
| S phase | Procarbazine<br>Hydroxyureas<br>Antimetabolites |
| G2 phase | Taxanes<br>Vinca alkaloids<br>Bleomycin |
| M phase | Taxanes and Vinca alkaloids |

**SPECIFIC MECHANISMS OF ACTION**

**ALKYLATING AGENTS**

Most alkylating agents are cell-cycle non specific. They interfere with DNA replication to prevent cancer cells from reproducing. The formation of carbonium ion intermediates is paramount to the action of alkylating drugs. These strong electrophiles form covalent bonds with various nucleophilic moieties. Alkylation of the 7-N atom of guanine causes incorrect base pairing and subsequent miscoding of DNA. A linear dose-response curve exists for these drugs. All alkylating agents can cause secondary cancers of which the most common is leukaemia.

**PLATINATING COMPOUNDS**

These agents work by cross-linking DNA subunits. The precise mechanism of action of platinating compounds is unknown, but they resemble the alkylating agents in that they are non-specific cell phase inhibitors. It is possible that they also stimulate the host's immune response. They are less likely than other alkylating agents to cause leukemia later on.

**VINCA ALKALOIDS**

Natural products and also fall under the group of "mitotic inhibitors". They bind to tubu- lin, inhibiting polymerization and thus the formation of microtubules. Cell division arrests in metaphase. Most are cell cycle specific acting in the M phase, but can damage cells in all phases. Microtubules are responsible for other functions besides the formation of mitotic spindles, including axonal transport of subcellular organelles.

**ANTIBIOTICS**

Derived from microorganisms and are not cell-cycle specific. They act during all phases of the cell cycle. They are very useful in slow growing tumors.
Actinomycin intercalates between base pairs, inhibiting DNA-dependent RNA synthesis.
Daunarubicin is thought to have the same mechanism of action.
Doxarubicin and Idarubicin are also thought to bind to cell membrane lipids and interact with Topoisomerase II. Bleomycin is effective in both cycling and static cells but is most effective in Phase G2

**ANTHRACENEDIONE (ANTHRACYCLINE ANALOGUES)**

Mitoxantrone is not cell-cylce specific but is mostly active during the S phase of mitosis. Binding to DNA base pairs initiates inhibition of DNA and RNA synthesis.

**METHYLHYDRAZINE DERIVATIVES**

Procarbazine acts via DNA alkylation and depolymerisation and is specific for the S phase of the cell cycle. It causes inhibition of the nucleic acids (DNA and RNA), and protein synthesis.

**BIOLOGICAL THERAPY**

**DEFINITION**

A type of treatment that uses substances made from living organisms to treat disease. These substances may occur naturally in the body or may be made in the laboratory. Some biological therapies stimulate or suppress the immune system to help the body fight cancer, infection and other diseases. Other biological therapies attack specific cancer cells, which may help keep them from growing or kill them. They may also lessen certain side effects caused by some cancer treatments. Biological therapies can be quite confusing. So far there isn't really a simple way of grouping them that is easy to follow. Some drugs belong to more than one group.

Types of biological therapy include immunotherapy (such as vaccines, cytokines and some antibodies), gene therapy and some targeted therapies. Other names for biological therapy include: biological response modifier therapy, biotherapy and BRM therapy.

The side effects associated with various biological therapies can differ by treatment type. However, pain, swelling, redness, itchiness and rash at the site of infusion or injection are fairly common with these treatments.

Several of the most important types of Biological therapy will be discussed briefly.

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# *Anti-inflammatory, Antipyretic, and Analgesic Agents*

**Inflammation** : is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents.

**Inflammation** : is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides. However, inappropriate activation of the immune system can result in inflammation, leading to immunemediated diseases such as rheumatoid arthritis (RA).

## PROSTAGLANDINS

The NSAIDs act by inhibiting the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires comprehension of the actions and biosynthesis of prostaglandins unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure.

### A. Role of prostaglandins as local mediators

Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action. Therefore, the prostaglandins do not circulate in the blood in significant concentrations. Thromboxanes and leukotrienes are related lipids that are synthesized from the same precursors as the prostaglandins.

### B. Synthesis of prostaglandins

**Arachidonic** acid is the primary precursor of the prostaglandins and related compounds. Arachidonic acid is present as a component of the phospholipids of cell membranes. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A2 via a process controlled by hormones and other stimuli. There are two major pathways in the synthesis of the eicosanoids from arachidonic acid, the cyclooxygenase and the lipoxygenase pathways.

## C. Actions of prostaglandins

Many of the actions of prostaglandins are mediated by their binding to a wide variety of distinct cell membrane receptors that operate via G-coupled proteins. Prostaglandins and their metabolites, produced endogenously in tissues, act as local signals that fine-tune the response of a specific cell type.

## D. Therapeutic uses of prostaglandins

Prostaglandins have a major role in modulating pain, inflammation, and fever. They also control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow. Prostaglandins are also among the chemical mediators that are released in allergic and inflammatory processes.

## E. Alprostadil

**Alprostadil** [al-PROS-ta-dil] is a **PGE1** that is naturally produced in tissues such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus. Therapeutically, alprostadil can be used to treat erectile dysfunction or to keep the ductus arteriosus open in neonates with congenital heart conditions until surgery is possible.

## F. Lubiprostone

**Lubiprostone** [loo-bee-PROS-tone] is a PGE1 derivative indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation.

## G. Misoprostol

**Misoprostol** [mye-soe-PROST-ole], a PGE1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment. Misoprostol interacts with prostaglandin receptors on parietal cells withinthe stomach, reducing gastric acid secretion.

## H. Prostaglandin F2 analogs

**Bimatoprost** [bih-MAT-o-prost], **latanoprost** [la-TAN-oh-prost], **tafluprost** [TAF-loo-prost], and travoprost [TRA-voe-prost] are PGF2a. analogs that are indicated for the treatment of open-angle glaucoma.

# NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. The class includes:

1-derivatives of salicylic acid (aspirin)

2-propionic acid

3-acetic acid

4-enolic acid

5-fenamates

6-the selective COX-2 inhibitor (celecoxib)

## **Aspirin and other NSAIDs

Aspirin can be thought of as a traditional NSAID, but it exhibits anti-inflammatory activity only at relatively high doses that are rarely used. It has gained much more usage at lower doses for the prevention of cardiovascular events such as stroke and myocardial infarction (MI). Aspirin is often differentiated from other NSAIDs, since it is an irreversible inhibitor of cyclooxygenase activity.

## Mechanism of action:

Aspirin is a weak organic acid that irreversibly acetylates (and, thus, inactivates) cyclooxygenase.

### a. Anti-inflammatory actions:

Cyclooxygenase inhibition diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation in which prostaglandins act as mediators.

**b. Analgesic action:**
PGE2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE2 synthesis, the sensation of pain can be decreased. As COX-2 is expressed during times of inflammation and injury, it is thought that inhibition of this enzyme is responsible for the analgesic activity of NSAIDs.

**c. Antipyretic action:**
The NSAIDs lower body temperature in patients with fever by impeding PGE2 synthesis and release. These agents essentially reset the "thermostat" toward normal.

**d-Cardiovascular applications:**
Aspirin is used to inhibit platelet aggregation. Low-dose aspirin inhibits COX-1-mediated production of TXA2, thereby reducing TXA2-mediated vasoconstriction and platelet aggregation and the subsequent risk of cardiovascular events.

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# Pharmacology

## Drugs used in the gastrointestinal diseases

- **Gastro-esophageal reflux disease(GERD):** is the return of the stomach's contents back up into the esophagus. also known as reflex esophagitis and commonly called heartburn.is destroyed the mucus lined the esophagus due to reflux of gastric content to esophagus due to weakness of lower esophageal sphincter(LES) ,intraabdominal pressure, poor resistance of esophagus mucus to the acid.
- **Goal of therapy :**

1. reduce gastric acidity
2. reduce gastric volume
3. increase gastric empty
4. enhance the closure of LES

- **Treatment of heartburn**

1. antacids
2. alginates(Gaviscon)
3. H2 receptor antagonists(H2RAs)
4. Proton pump inhibitor (PPIs)

## 1. Antacids:

- containing AL salts AL (OH)2 ,Mg salts Mg(OH)2,Ca carbonate, Na bicarbonate

Are weak basic compounds that neutralize hydrochloric acid into the gastric secretion by **mechanism:-**

Weak base(antacid) + HCL =water and salt →decrease acidity ↑PH

**Used in**

Symptomatic management of gastro-intestinal disorders associated with gastric hyperacidity as dyspepsia{ Dyspepsia Greek word (hard or difficult digestion)}, GERD, and peptic ulcer disease .

*Antacids provide immediate symptomatic relief for mild GERD and are often used in concurrently with other acid suppressing therapies.

*Best given when symptoms occur their duration short (30 min)on empty stomach, but duration extended 3 hr. when given with or within 1 hr. after a meal.

*rapid onset , short duration

## Antacids:


AL hydroxide + Mg hydroxide


AL hydroxide + Mg hydroxide
+simethicone


Chewable tab Ca Carbonate + Mg Carbonate

## Antacids:


Sodium bicarbonate+ citric acid
+tartaric acid


Sodium Carbonate+ citric acid

## Antacids:

*antacids may be formulated with other active ingredient like Simethicon(anti gas)(Maalox plus)to control gas or alginic acid (Gaviscone)to act as physical barrier to acid.

## Drug interaction:

- antacid can bind to concomitantly administered drugs and interfere with absorption of drugs (e.g.tetracycline and ciprofloxacin) because antacid chelate with antibiotic to form an insoluble inactive complex. So administration of ciprofloxacin 2hr before antacid.
- Antacid ↑PH of stomach, thus cause premature release of enteric coated tab in stomach rather than the intestine.

*Antacid in patient with renal failure should be avoided →antacid AL, Mg, small amount absorbed systemically and accumulate in body→ toxicity

## Side effects:

AL- containing antacid tend to be constipating, Mg containing antacid tend to cause diarrhea. thus combination products of AL& Mg salts cause minimum bowel disturbances

Antacid containing Sodium bicarbonate should be avoided in patient if sodium intake should restricted(congestive heart failure ,hypertention)

# Alginate

Alginate contain antacids form a sponge like matrix that float on the top of the stomach contents so when reflex occur alginate rather than acids will be reflexed &irritation is minimized ,protects the esophageal mucosa from acid attach.

Alginate preparations are also commonly combined with antacids to help neutralize stomach acid .

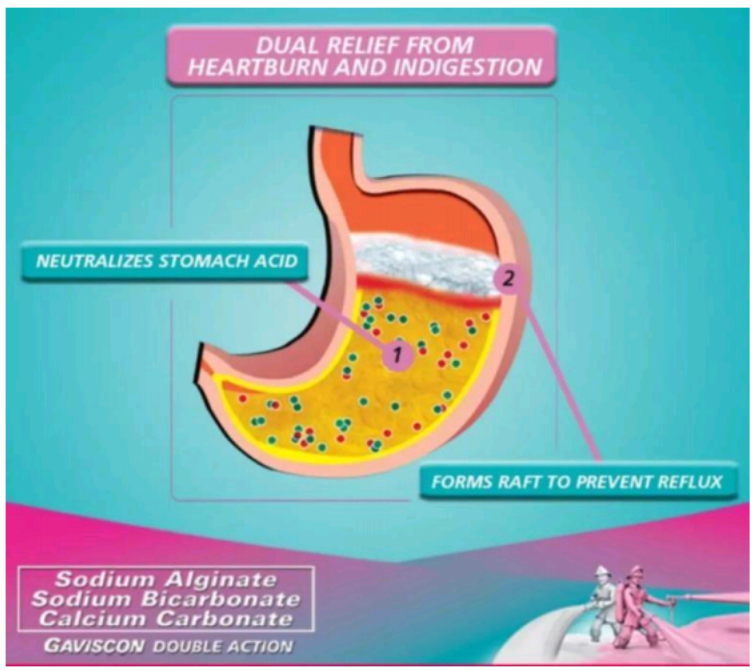
Gaviscon as suspension ,chewable tab. 10ml, 2-4 tab every 6 hr. after food

Used treat GERD, dyspepsia


Sodium alginate

NA bicarbonate

Ca bicarbonate



## H2 Receptor Antagonists (H2RAs)

H2 receptor is one type of histamine receptor located in gastric mucosa ,which has excitatory effect, when histamine binding by H2 receptor increase the secretion of HCL.

H2RAs include: cimetidine, ranitidine, famotidine, nizatidine.

**Uses:**

GERD, gastric and duodenal ulcer , non-ulcer dyspepsia, prevention of bleeding from stress related gastritis.

*H2RAs competitively and selectively inhibit the action of histamine on the H2recepters of the parietal cells , thus reducing both basal and stimulated gastric acid secretion.

*Famotidine has the greatest potency, followed by nizatidine ,ranitidine, cimetidine.

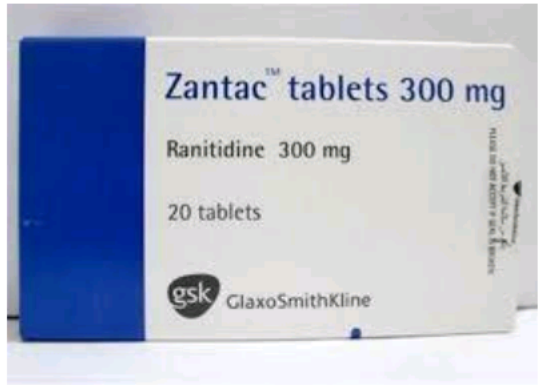
H2RAs are taken on empty stomach( 1hr before ameal)

They are remarkably safe and well tolerated the most common

# H2 Receptor Antagonists

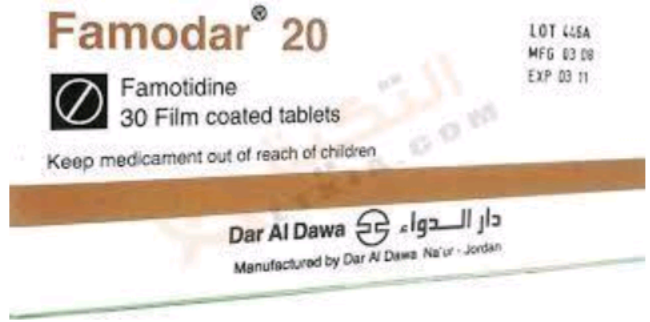


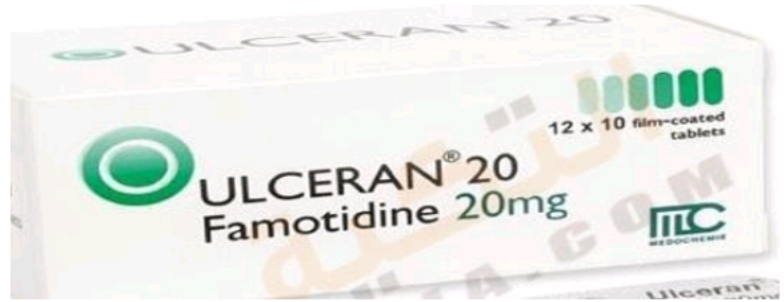
**Cimitidine 200,400,tab, syrup,ampoule**





**Ranitidine 150,300 tab,syrup, ampoule**




**Famotidine,20,40 tab**

## H2 Receptor Antagonists (H2RAs)

**adverse effects:** headache ,somnolence, fatigue ,dizziness, constipation or diarrhea.

Cimetidine has weak anti androgenic effects, its use in high doses (hypersecretory conditions)has been associated with gynecomastia in men .this is reversible with discontinuation of medication or by switching to another H2RAs.

Cimetidine inhibits several CYP450 isoenzymes ,resulting in numerous drug interactions(theophylline ,warfarin, clopidogrel, phenytoin, propranolol)

Ranitidine less potential for hepatic CYP450 drug interaction

Famotidine, nizatidine do not interact with drugs metabolized by hepatic CYP450

PPI preferred are superior to H2RAs in reducing gastric acid secretion &mucosal healing. PPIs suppress gastric acid more strongly , for a longer period.

## Proton Pump Inhibitors (PPIs)

PPIs are the most potent inhibitors of gastric acid secretion and include

Omeprazole, Lansoprazole,Rabeprazole,Pantoprazole,Esomeprazole,Dexlanzoprazole.

*PPIs block gastric acid secretion by inhibiting hydrogen potassium adenosine triphosphate(H-K ATPase )in gastric parietal cells ,which results in profound and long lasting anti-secretory effects.

*PPIs irreversibly inhibit proton pump H-K ATPase.

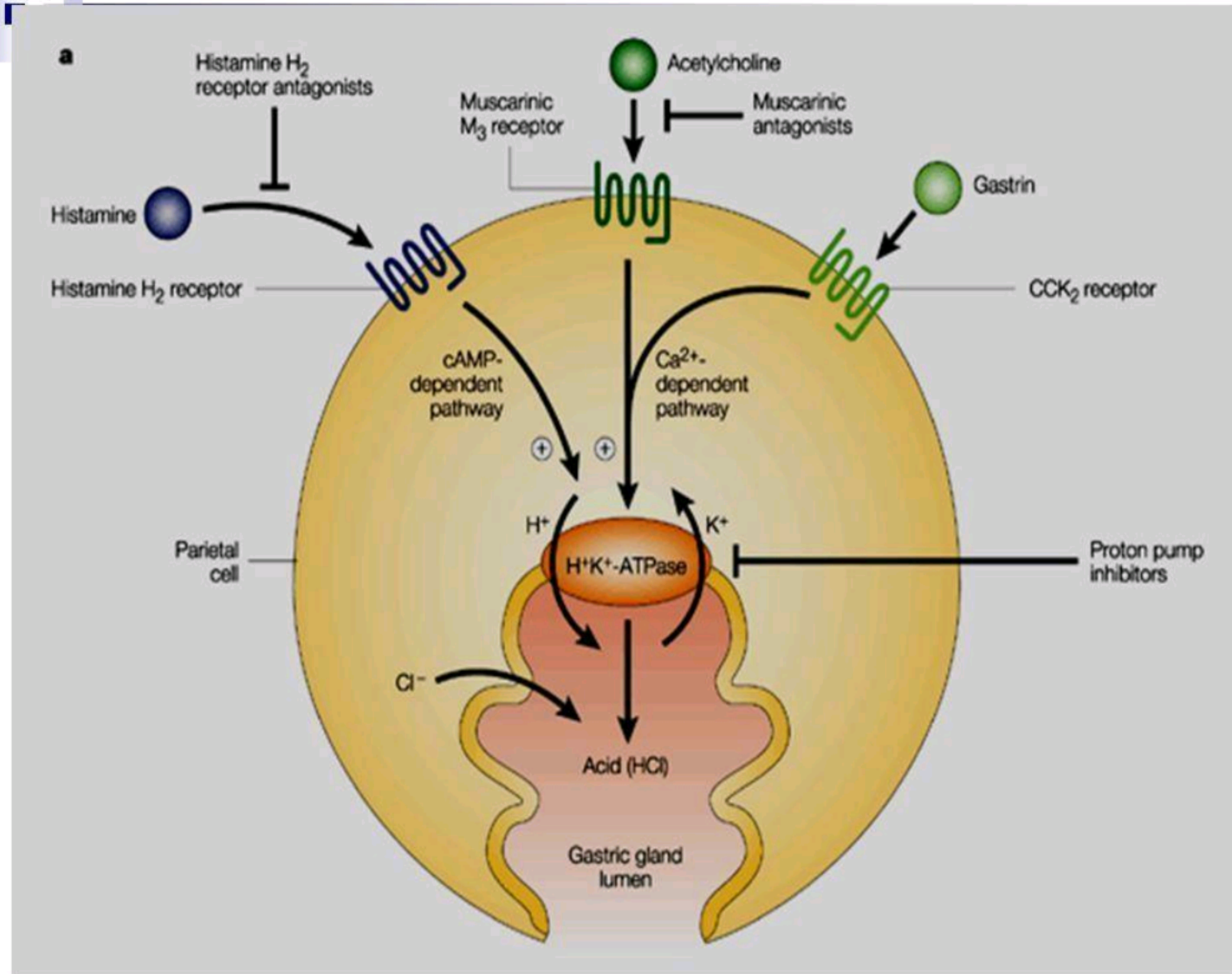
## Uses

-Gastric and duodenal ulcer

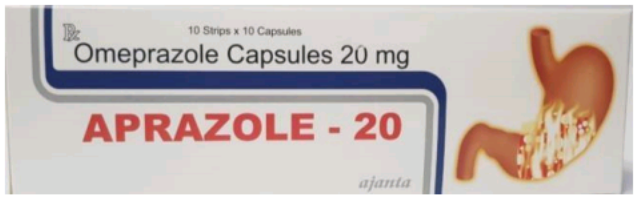
-In combination with antibacterial for the eradication of Helicobacter Pylori(abacteria that is common cause of ulcer)

-PPIs can be used in treatment of dyspepsia and GERD.

-prevention and treatment of NSAIDs-associated ulcers.


a
Histamine $H_2$ receptor antagonists
Acetylcholine
Muscarinic $M_3$ receptor
Muscarinic antagonists
Gastrin
Histamine
Histamine $H_2$ receptor
$CCK_2$ receptor
cAMP-dependent pathway
$Ca^{2+}$-dependent pathway
$H^+$
$K^+$
Parietal cell
$H^+K^+$-ATPase
Proton pump inhibitors
$Cl^-$
Acid (HCl)
Gastric gland lumen

# Proton Pump Inhibitors





10,20,40,cap., vial

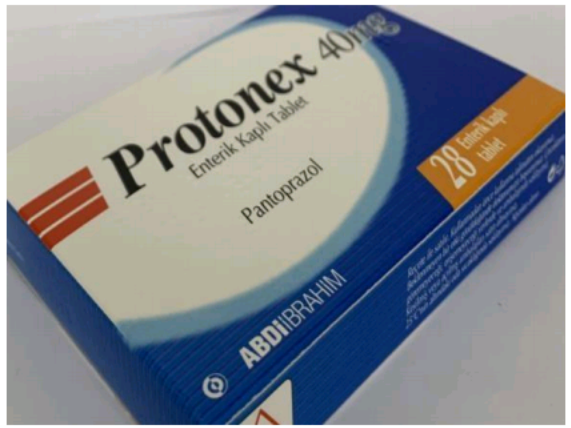


**Lansoprazole**
**15,30 cap**



**Rabeprazole 10,20 tab**

# Proton Pump Inhibitors


**Pantoprazole 20,40 tab**


**Esomeprazole 20,40 tab , vial**

## Proton Pump Inhibitors

PPIs given on empty stomach(food affects their absorption), they should be given 30-60 minute before food intake (once daily in the morning or may be twice daily one in the morning and the second in the at night.)

*PPIs→↓acid secretion 90 %

## Adverse effects

- Headache ,dizziness, diarrhea , constipation ,nausea ,vit B12 deficiency.
- All PPIs can ↓absorption of drugs as ketoconazole, itraconazole that require acidic environment for absorption
- Esmoprazole ,omeprazole , lansoprazole reduce the antiplatelet effect of clopidogrel .
- Omeprazole may inhibit metabolism of clopidogrel, warfarin, diazepam, phenytoin
- Rabeprazole, pantoprazole have no significant drug interaction.

## Promotility Agents or Prokinetic drugs

(**Prokinetic** agents) have significant potential clinical usefulness.

Agents that increase lower esophageal sphincter pressures may be useful for GERD.

Drugs that improve gastric emptying may be helpful for gastroparesis and postsurgical gastric emptying delay. constipation, heartburn, nausea, vomiting.

**Metoclopramide & Domperidone**

Metoclopramide and domperidone are dopamine $D_2$ receptor antagonists. Within the gastrointestinal tract activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of these agents.

These agents increase, increase lower esophageal sphincter pressure, and enhance gastric emptying .Metoclopramide and domperidone also block dopamine $D_2$ receptors in the chemoreceptor trigger zone of the medulla resulting in potent antinausea and antiemetic action

## Metoclopramide & Domperidone

**Clinical Uses**

-Gastroesophageal Reflux Disease

-Impaired Gastric Emptying

-Non ulcer Dyspepsia

-Prevention of Vomiting

**Adverse Effects**

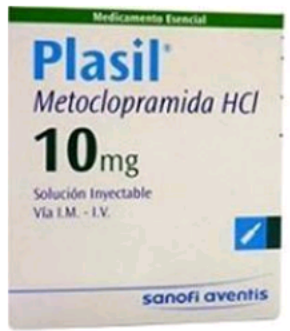
- The most common adverse effects of metoclopramide involve the central nervous system. Restlessness, drowsiness, insomnia, anxiety, and agitation occur in 10–20% of patients, especially the elderly.

Extrapyramidal effects (dystonias, akathisia, parkinsonian features) due to central dopamine receptor blockade occur acutely in 25% of patients given high doses and in 5% of patients receiving long-term therapy. sometimes irreversible, has developed in patients treated for a prolonged period with metoclopramide. For this reason, long-term use should be avoided unless absolutely necessary, especially in the elderly.

Elevated prolactin levels (caused by both metoclopramide and domperidone) can cause galactorrhea, gynecomastia.

- Domperidone is extremely well tolerated. Because it does not cross the blood-brain barrier to a significant degree, neuropsychiatric and extrapyramidal effects are rare.

# Metoclopramide & Domperidone


Metoclopramide 5,10 tab, syrup,ampoule



**Domperidone 10 mg tab**

## Mucosal Protective Agents

- The gastroduodenal mucosa has evolved a number of defense mechanisms to protect itself against the noxious effects of acid and pepsin.
- Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin.
- Epithelial bicarbonate secretion establishes a pH gradient within the mucous layer in which the pH ranges from 7 at the mucosal surface to 1–2 in the gastric lumen.
- Blood flow carries bicarbonate and vital nutrients to surface cells.
- Mucosal prostaglandins appear to be important in stimulating mucus and bicarbonate secretion and mucosal blood flow. A number of agents that potentiate these mucosal defense mechanisms are available for the prevention and treatment of acid-peptic disorders.

### 1. Sucralfate

- Sucralfate is a salt of sucrose complexed to sulfated aluminum hydroxide. In water or acidic solutions it forms a viscous, tenacious paste that binds selectively to ulcers or erosions for up to 6 hours.
- It is also binds to proteins in the base of ulcers or erosion, forming a physical barrier that restricts further caustic damage and stimulates mucosal prostaglandin and bicarbonate secretion.
- Sucralfate used for prophylaxis of stress ulcer, Treat gastric ulcer.

Adverse effect :constipation

## 2. Prostaglandin Analogs

- The human gastrointestinal mucosa synthesizes a number of prostaglandins ,the primary ones are prostaglandins E and F. **Misoprostol,** a methyl analog of PGE1 , has been approved for gastrointestinal conditions. The serum half-life is less than 30 minutes; hence, it must be administered 3–4 times daily
- Misoprostol has both acid inhibitory and mucosal protective properties.
- It is believed to stimulate mucus and bicarbonate secretion and enhance mucosal blood flow. In addition, it binds to a prostaglandin receptor on parietal cells causing modest acid inhibition.

### Clinical Uses

- It is approved for prevention of NSAID-induced ulcers in high-risk patients; however, misoprostol has never achieved widespread use owing to its high adverse-effect profile and need for multiple daily dosing.
- Proton pump inhibitors may be as effective as and better tolerated than misoprostol for this indication. Cyclooxygenase-2-selective NSAIDs, which may have less gastrointestinal toxicity .

### Adverse Effects

-Diarrhea and cramping abdominal pain

-stimulates uterine contractions

## 3. Bismuth Compounds

**Bismuth subsalicylate,** containing bismuth and salicylate, and **bismuth subcitrate potassium**

Bismuth chelate with protein material in the ulcer base forming a coating to ulcers and erosions, creating a protective layer against acid and pepsin.. Bismuth compounds have direct antimicrobial activity against *H pylori.*

### Clinical Uses

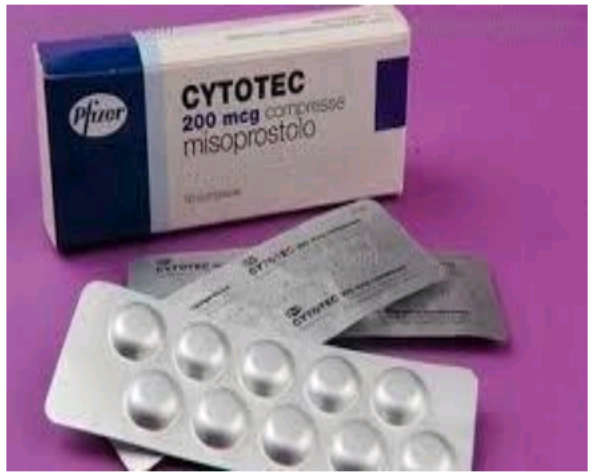
-Bismuth compounds are used in 4 drug regimens for the eradication of *H pylori* infection.

-For gastric and duodenal ulcer

### Adverse Effects

Bismuth causes harmless blackening of the stool, darkening of the tongue,teeth.


Sucralfate tab (Gastrofait)




misoprostol (cytotic)


**Bismuth subsalicylate**

## Peptic ulcer

**Peptic ulcer** :break in the gastric or duodenal mucosa that extend into deeper layers.

Due to imbalance between cell destructive(HCL, pepsin , H. Pylori infection, NSAID ingestion)and cell protective effects(mucosal blood flow, mucus, mucosal bicarbonate secretion).

## Causes

-Helicobacter Pylori infection(60-90%)
-Chronic use of NSAIDs
-Stress related mucosal damage
-Smoking
-Zollinger-Ellison Syndrome(ZES)(↑gastrin hormone due to tumers→↑too much stomach acid)
-Genetic

## Peptic ulcer

### Many ways for healing and prevent recurrence of ulcer:

1.Reduction of acid secretion( H2RAs ,PPIs, antimuscarinic drug)

2.neutralization of secreted acid by antacid

3.enhancement of mucosal resistance: protecting the base of peptic ulcer (bismuth,sucralfate), Eradicating H-Pylori

4. cytoprotection(misoprostol)

### Treatment of Eradicating H-Pylori:

1. For 14 days metronidazole and either (clarithromycin ,amoxycillin, or tetracycline)combined with suppression of acid secretion (omeprazole)

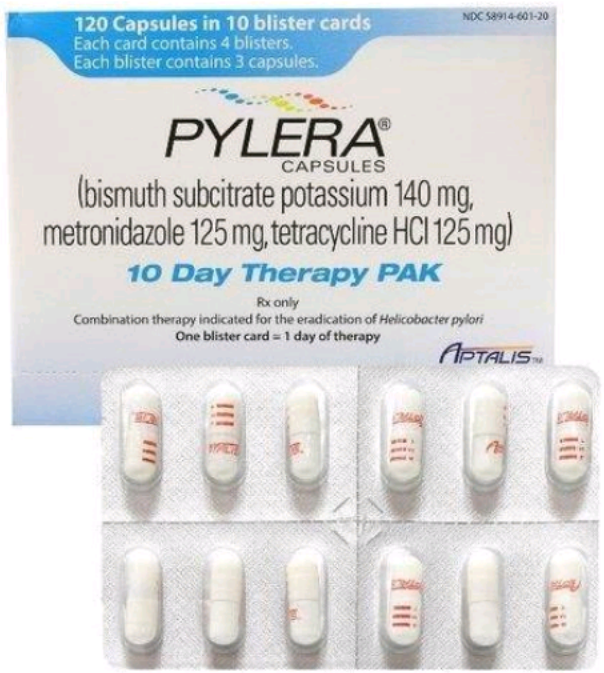
2. Bismuth, metronidazole, either (clarithromycin ,amoxycillin, or tetracycline)combined with (omeprazole) For 10-14 days.

## Eradicating H-Pylori:


Clarithromycin

Tinidazole

lansoprazole




Bismuth subcitrate potassium

Metronidazole

tetracycline

# THANK YOU